09/285,429

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     (FILE 'HOME' ENTERED AT 15:34:20 ON 20 DEC 2000)

     FILE 'BIOSIS, MEDLINE, SCISEARCH, USPATFULL' ENTERED AT 15:35:17 ON 20
     DEC 2000
                  E SHIRLEY BRET A/AU
L1                1 S E2
L2                4 S E3
L3                1 S E4
L4            49196 S IGF OR (INSULIN GROWTH FACTOR)
L5                2 S L4 AND (L1 OR L2 OR L3)
                  E MANINDER HORA S/AU
L6               11 S E1
L7              907 S L6 AND IGF OR (INSULIN GROWTH FACTOR)
L8                0 S L7 AND (SUCCINATE BUFFER)
L9               18 S L7 AND (SUCCINATE)
L10              14 S L9 AND BUFFER
```

L5 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1998:422060 BIOSIS
DN PREV199800422060
TI Issues in liquid formulation development for insulin-like growth factor I (**IGF**-I.
AU **Shirley, Bret A.**; Bajwa, Kamaljit K.; Lone, Timothy A.; Arellano, Sandra L.; Hora, Maninder S.
CS Dep. Formulation, Chiron Corp., Emeryville, CA 94521 USA
SO Abstracts of Papers American Chemical Society, (1998) Vol. 216, No. 1-3, pp. BIOT 7.
Meeting Info.: 216th National Meeting of the American Chemical Society Boston, Massachusetts, USA August 23-27, 1998 American Chemical Society . ISSN: 0065-7727.
DT Conference
LA English

L5 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1998:105333 BIOSIS
DN PREV199800105333
TI A sustained-release system for efficient encapsulation with high loading of insulin-like growth factor-I (**IGF**-I.
AU Qiang, Ye (1); Stevenson, Mark (1); Asherman, John (1); Chen, Sharon; **Shirley, Bret**; Katre, Nandini (1)
CS (1) Dep. Tech. Corp., San Diego, CA 92121 USA
SO Pharmaceutical Research (New York), (Nov., 1997) Vol. 14, No. 11 SUPPL., pp. S469.
Meeting Info.: Annual Meeting of the American Association of Pharmaceutical Scientists Boston, Massachusetts, USA November 2-6, 1997 American Association of Pharmaceutical Scientists . ISSN: 0724-8741.
DT Conference
LA English

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L5 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1998:105333 BIOSIS
DN PREV199800105333
TI A sustained-release system for efficient encapsulation with high loading of insulin-like growth factor-I (**IGF**-I.
AU Qiang, Ye (1); Stevenson, Mark (1); Asherman, John (1); Chen, Sharon; **Shirley, Bret**; Katre, Nandini (1)
CS (1) Dep. Tech. Corp., San Diego, CA 92121 USA
SO Pharmaceutical Research (New York), (Nov., 1997) Vol. 14, No. 11 SUPPL., pp. S469.
Meeting Info.: Annual Meeting of the American Association of Pharmaceutical Scientists Boston, Massachusetts, USA November 2-6, 1997 American Association of Pharmaceutical Scientists
. ISSN: 0724-8741.
DT Conference
LA English
CC Pharmacology - General *22002
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Endocrine System - General *17002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Endocrine System *22016
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
IT Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Pharmaceuticals (Pharmacology)
IT Chemicals & Biochemicals
insulin-like growth factor-I: hormone - drug, metabolic - drug, pharmaceuticals
IT Methods & Equipment
encapsulation: high loading; peptide delivery; sustained-release system: pharmacological method; DepoTech drug delivery system: pharmacological method
IT Miscellaneous Descriptors
Meeting Abstract; Meeting Poster
RN 67763-96-6 (INSULIN-LIKE GROWTH FACTOR-I)

L5 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2000 BIOSIS
TI A sustained-release system for efficient encapsulation with high loading of insulin-like growth factor-I (**IGF**-I.
AU Qiang, Ye (1); Stevenson, Mark (1); Asherman, John (1); Chen, Sharon; **Shirley**, **Bret**; Katre, Nandini (1)

=> d l11 1-14

L11 ANSWER 1 OF 14 USPATFULL
AN 2000:160610 USPATFULL
TI Biodegradable terephthalate polyester-poly (phosphonate) compositions, articles, and methods of using the same
IN Mao, Hai-quan, Towson, MD, United States
Leong, Kam W., Ellicott City, MD, United States
Zhao, Zhong, Ellicott City, MD, United States
Dang, Wenbin, Ellicott City, MD, United States
English, James P., Chelsea, AL, United States
Nowotnik, David P., Kingsville, MD, United States
PA Guilford Pharmaceuticals Inc., Baltimore, MD, United States (U.S. corporation)
Johns Hopkins University School of Medicine, Baltimore, MD, United States (U.S. corporation)
PI US 6153212 20001128
AI US 1998-165375 19981002 (9)
DT Utility
LN.CNT 1448
INCL INCLM: 424/426.000
INCLS: 514/772.300
NCL NCLM: 424/426.000
NCLS: 514/772.300
IC [7]
ICM: A61F002-02
ICS: A61K047-30
EXF 424/426; 514/772.3
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 2 OF 14 USPATFULL
AN 2000:128360 USPATFULL
TI Methods and compositions for stimulating neurite growth
IN Armistead, David M., Maynard, MA, United States
PA Vertex Pharmaceuticals Incorporated, Cambridge, MA, United States (U.S. corporation)
PI US 6124328 20000926
AI US 1997-795956 19970228 (8)
RLI Division of Ser. No. US 1995-486004, filed on 8 Jun 1995, now patented, Pat. No. US 5654332
DT Utility
LN.CNT 1344
INCL INCLM: 514/354.000
INCLS: 514/357.000; 514/360.000; 514/365.000; 514/374.000; 514/385.000; 514/192.000
NCL NCLM: 514/354.000
NCLS: 514/192.000; 514/357.000; 514/360.000; 514/365.000; 514/374.000; 514/385.000
IC [7]
ICM: A61K031-44
ICS: A61K031-41; A61K031-415; A61K031-43
EXF 514/354; 514/357; 514/360; 514/365; 514/374; 514/385; 514/192
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 3 OF 14 USPATFULL
AN 2000:70810 USPATFULL
TI Use of IGF-I for the treatment of renal insufficiencies, steriod

toxicity and related indications
IN Acott, Philip D., Halifax, Canada
Crocker, John F. S., Halifax, Canada
PA Dalhousie University, Halifax, Canada (non-U.S. corporation)
PI US 6071880 20000606
AI US 1999-307005 19990507 (9)
RLI Division of Ser. No. US 1997-933196, filed on 16 Sep 1997, now patented,
Pat. No. US 5985830 which is a continuation-in-part of Ser. No. US 1996-710331, filed on 16 Sep 1996, now abandoned
DT Utility
LN.CNT 1306
INCL INCLM: 514/012.000
NCL NCLM: 514/012.000
IC [7]
ICM: A61K038-00
EXF 514/12
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 4 OF 14 USPATFULL
AN 2000:31444 USPATFULL
TI Methods and compositions for stimulating neurite growth
IN Armistead, David M., Maynard, MA, United States
PA Vertex Pharmaceuticals Incorporated, Cambridge, MA, United States (U.S. corporation)
PI US 6037370 20000314
AI US 1995-486004 19950608 (8)
DT Utility
LN.CNT 1325
INCL INCLM: 514/533.000
INCLS: 514/534.000; 514/330.000; 514/423.000; 514/428.000; 514/438.000; 514/538.000; 514/547.000; 514/549.000; 514/551.000; 514/465.000; 514/466.000
NCL NCLM: 514/533.000
NCLS: 514/330.000; 514/423.000; 514/428.000; 514/438.000; 514/465.000; 514/466.000; 514/534.000; 514/538.000; 514/547.000; 514/549.000; 514/551.000
IC [7]
ICM: A61K031-235
ICS: A61K031-24; A61K031-40; A61K031-38
EXF 514/533; 514/534; 514/330; 514/423; 514/428; 514/438; 514/538; 514/547; 514/548; 514/551; 514/465; 514/466
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 5 OF 14 USPATFULL
AN 1999:146529 USPATFULL
TI Use of IGF-I for the treatment of kidney disorders
IN Acott, Philip D., Halifax, Canada
Crocker, John F. S., Halifax, Canada
PA Dalhousie University, Halifax, Canada (non-U.S. corporation)
PI US 5985830 19991116
AI US 1997-933196 19970916 (8)
RLI Continuation of Ser. No. US 1996-710331, filed on 16 Sep 1996, now abandoned
DT Utility
LN.CNT 1205
INCL INCLM: 514/012.000
NCL NCLM: 514/012.000
IC [6]
ICM: A61K038-00
EXF 514/12
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 6 OF 14 USPATFULL
AN 1999:117030 USPATFULL
TI Pharmaceutical multiple unit particulate formulation in the form of

coated cores
IN Norling, Tomas, Lyngby, Denmark
Jensen, Lone Norgaard, Soborg, Denmark
Hansen, Jens, Allerod, Denmark
PA Dumex-Alpharma A/S, Copenhagen, Denmark (non-U.S. corporation)
PI US 5958458 19990928
AI US 1995-509107 19950801 (8)
RLI Continuation-in-part of Ser. No. US 1994-268037, filed on 29 Jun 1994
PRAI DK 1994-695 19940615
DT Utility
LN.CNT 2292
INCL INCLM: 424/490.000
INCLS: 424/489.000; 424/468.000; 424/469.000; 424/466.000; 514/951.000
NCL NCLM: 424/490.000
NCLS: 424/466.000; 424/468.000; 424/469.000; 424/489.000; 514/951.000
IC [6]
ICM: A61K009-16
ICS: A61K047-02
EXF 424/422; 424/458-462; 424/469-470; 424/489-502; 424/421; 424/687; 424/466; 424/471; 514/951; 514/952
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 7 OF 14 USPATFULL
AN 1999:113787 USPATFULL
TI Use of fatty acid esters as bioadhesive substances
IN Hansen, Jens, Allerod, Denmark
Nielsen, Lise Sylvest, Copenhagen .O slashed., Denmark
Norling, Tomas, Lyngby, Denmark
PA GS Development AB, Malmo, Sweden (non-U.S. corporation)
PI US 5955502 19990921
AI US 1997-829496 19970327 (8)
RLI Division of Ser. No. US 1997-462222, filed on 5 Jun 1997
PRAI DK 1994-37 19940330
DT Utility
LN.CNT 2331
INCL INCLM: 514/558.000
INCLS: 514/559.000; 514/560.000; 424/407.000
NCL NCLM: 514/558.000
NCLS: 424/407.000; 514/559.000; 514/560.000
IC [6]
ICM: A61K037-02
ICS: A61K037-06
EXF 424/407; 514/559; 514/560; 514/558
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 8 OF 14 USPATFULL
AN 1999:92670 USPATFULL
TI Compounds with improved multi-drug resistance activity
IN Armistead, David M., Maynard, MA, United States
Saunders, Jeffrey O., Acton, MA, United States
PA Vertex Pharmaceuticals Incorporated, Cambridge, MA, United States (U.S. corporation)
PI US 5935954 19990810
AI US 1997-961551 19971030 (8)
RLI Division of Ser. No. US 1996-626259, filed on 29 Mar 1996, now patented,
Pat. No. US 5717092
DT Utility
LN.CNT 2309
INCL INCLM: 514/235.200
INCLS: 514/235.500; 514/237.200; 514/343.000; 514/422.000; 514/423.000; 544/124.000; 544/141.000; 544/143.000; 544/059.000; 544/186.000; 544/187.000; 544/193.000; 544/194.000; 544/360.000; 544/372.000; 546/279.100; 548/517.000; 548/518.000; 548/531.000; 548/536.000
NCL NCLM: 514/235.200
NCLS: 514/235.500; 514/237.200; 514/343.000; 514/422.000; 514/423.000;

544/059.000; 544/124.000; 544/141.000; 544/143.000; 544/186.000;
544/187.000; 544/193.000; 544/194.000; 544/360.000; 544/372.000;
546/279.100; 548/517.000; 548/518.000; 548/531.000; 548/536.000
IC [6]
ICM: C07D211-60
ICS: C07D401-12; C07D409-12; A61K031-445
EXF 548/517; 548/518; 548/531; 548/536; 546/279.1; 544/124; 544/141;
544/143; 514/235.2; 514/235.5; 514/237.2; 514/343; 514/422; 514/423
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 9 OF 14 USPATFULL
AN 1998:147451 USPATFULL
TI Methods and compositions for stimulating neurite growth
IN Zelle, Robert E., Stow, MA, United States
Su, Michael, Newton, MA, United States
PA Vertex Pharmaceuticals Incorporated, Cambridge, MA, United States (U.S.
corporation)
PI US 5840736 19981124
AI US 1996-748447 19961113 (8)
DT Utility
LN.CNT 1091
INCL INCLM: 514/332.000
INCLS: 514/012.000; 514/341.000
NCL NCLM: 514/332.000
NCLS: 514/012.000; 514/341.000
IC [6]
ICM: A61K031-44
ICS: A61K038-18
EXF 514/12; 514/332; 514/341
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 10 OF 14 USPATFULL
AN 1998:115749 USPATFULL
TI Methods and compositions for stimulating neurite growth
IN Zelle, Robert E., Stow, MA, United States
Su, Michael, Newton, MA, United States
PA Vertex Pharmacueticals Incorporated, Cambridge, MA, United States (U.S.
corporation)
PI US 5811434 19980922
AI US 7484488 19961113 (8)
DT Utility
LN.CNT 1151
INCL INCLM: 514/307.000
INCLS: 514/314.000; 514/315.000; 514/318.000; 514/330.000; 514/332.000;
514/351.000; 514/237.200; 546/139.000; 546/192.000; 546/193.000;
546/194.000; 546/245.000; 546/256.000; 546/300.000; 544/129.000
NCL NCLM: 514/307.000
NCLS: 514/237.200; 514/314.000; 514/315.000; 514/318.000; 514/330.000;
514/332.000; 514/351.000; 544/129.000; 546/139.000; 546/192.000;
546/193.000; 546/194.000; 546/245.000; 546/256.000; 546/300.000
IC [6]
ICM: C07D211-60
ICS: A61K031-215
EXF 544/129; 546/153; 546/192; 546/193; 546/194; 546/245; 546/139; 546/256;
546/300; 514/251.2; 514/314; 514/315; 514/318; 514/330; 514/307;
514/332; 514/351
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 11 OF 14 USPATFULL
AN 1998:82771 USPATFULL
TI Methods for stimulating neurite growth with piperidine compounds
IN Zelle, Robert E., Stow, MA, United States
Su, Michael, Newton, MA, United States
PA Vertex Pharmaceuticals Incorporated, Cambridge, MA, United States (U.S.
corporation)
PI US 5780484 19980714

AI US 1996-749114 [redacted]961113 (8)
DT Utility
LN.CNT 868
INCL INCLM: 514/316.000
INCLS: 514/317.000; 514/318.000; 514/237.200; 514/314.000; 514/012.000
NCL NCLM: 514/316.000
NCLS: 514/012.000; 514/237.200; 514/314.000; 514/317.000; 514/318.000
IC [6]
ICM: A61K031-445
ICS: A61K031-535; A61K031-47; A61K038-18
EXF 514/316; 514/317; 514/318; 514/237.2; 514/314; 514/12
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 12 OF 14 USPATFULL
AN 1998:14934 USPATFULL
TI Compounds with improved multi-drug resistance activity
IN Armistead, David M., Maynard, MA, United States
Saunders, Jeffrey O., Acton, MA, United States
PA Vertex Pharmaceuticals Inc., Cambridge, MA, United States (U.S. corporation)
PI US 5717092 19980210
AI US 1996-626259 19960329 (8)
DT Utility
LN.CNT 2110
INCL INCLM: 544/129.000
INCLS: 544/360.000; 546/193.000; 546/194.000; 546/207.000; 546/208.000; 546/213.000; 546/226.000; 546/227.000
NCL NCLM: 544/129.000
NCLS: 544/360.000; 546/193.000; 546/194.000; 546/207.000; 546/208.000; 546/213.000; 546/226.000; 546/227.000
IC [6]
ICM: C07D211-06
ICS: C07D211-36; C07D211-60
EXF 544/129; 546/193; 546/194; 546/207; 546/208; 546/213; 546/226; 546/227
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 13 OF 14 USPATFULL
AN 97:68499 USPATFULL
TI Methods and compositions for stimulating neurite growth
IN Armistead, David M., Maynard, MA, United States
PA Vertex Pharmaceuticals Incorporated, Cambridge, MA, United States (U.S. corporation)
PI US 5654332 19970805
AI US 1995-486004 19950608 (8)
DT Utility
LN.CNT 1225
INCL INCLM: 514/533.000
INCLS: 514/534.000; 514/330.000; 514/423.000; 514/428.000; 514/438.000; 514/538.000; 514/547.000; 514/549.000; 514/551.000; 514/465.000; 514/466.000
NCL NCLM: 514/533.000
NCLS: 514/330.000; 514/423.000; 514/428.000; 514/438.000; 514/465.000; 514/466.000; 514/534.000; 514/538.000; 514/547.000; 514/549.000; 514/551.000
IC [6]
ICM: A61K031-235
ICS: A61K031-24; A61K031-40; A61K031-38; A61K031-44; A61K031-225; A61K031-22; A61K031-36
EXF 514/533; 514/534; 514/330; 514/423; 514/428; 514/438; 514/538; 514/547; 514/549; 514/551; 514/465; 514/466
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 14 OF 14 USPATFULL
AN 88:13183 USPATFULL
TI Recombinant growth hormone releasing factor
IN Bhatt, Ram S., Nutley, NJ, United States

Collier, Kennet[redacted]., Rockaway, NJ, United States
Crowl, Robert M[redacted] Little Falls, NJ, United State[redacted]
Poonian, Mohindar S., West Caldwell, NJ, United States
PA Hoffmann-La-Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 4728609 19880301
AI US 1985-778779 19850924 (6)
RLI Continuation of Ser. No. US 1983-456660, filed on 10 Jan 1983, now abandoned And a continuation-in-part of Ser. No. US 1982-439168, filed on 4 Nov 1982, now abandoned
DT Utility
LN.CNT 885
INCL INCLM: 435/068.000
INCLS: 435/070.000; 435/172.300; 435/253.000; 435/320.000; 935/013.000; 536/027.000
NCL NCLM: 435/069.400
NCLS: 435/252.330; 435/320.100; 536/023.510; 536/024.100; 536/024.200; 930/120.000
IC [4]
ICM: C12P021-00
ICS: C12P021-02; C12N015-00; C12N001-20; C12N001-00; C07H015-12
EXF 435/172.3; 435/68-70; 435/253; 435/317; 935/13; 536/27
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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L11 ANSWER 1 OF 14 USPATFULL
DETD . . . solubility in water are generally subject to hydrolysis rather than polymerization. Phase transfer catalysts, such as crown ethers or tertiary **ammonium** chloride, can be used to bring the ionized diol to the interface to facilitate the polycondensation reaction. The yield and. . .
DETD . . . dextromethorphan, dextro-methorphan hydrobromide, noscapine, carbetapentane citrate, and chlophedianol hydrochloride; (c) antihistamines such as chlorpheniramine maleate, phenindamine tartrate, pyrilamine maleate, doxylamine **succinate**, and phenyltoloxamine citrate; (d) decongestants such as phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine hydrochloride, and ephedrine; (e) various alkaloids such as codeine phosphate, codeine sulfate and morphine; (f) mineral supplements such as **potassium** chloride, zinc chloride, calcium carbonates, magnesium oxide, and other alkali metal and alkaline earth metal salts; (g) ion exchange resins.
.
DETD . . . antineoplastics; electrolytic and renal agents, such as acidifying agents, alkalinizing agents, diuretics, carbonic anhydrase inhibitor diuretics, loop diuretics, osmotic diuretics, **potassium**-sparing diuretics, thiazide diuretics, electrolyte replacements, and uricosuric agents; enzymes, such as pancreatic enzymes and thrombolytic enzymes; gastrointestinal agents, such as. . .
DETD . . . antineoplastics, such as fluorouracil (5-FU); (63) electrolytic and renal agents, such as lactulose; (64) loop diuretics, such as furosemide; (65) **potassium**-sparing diuretics, such as triamterene; (66) thiazide diuretics, such as hydrochlorothiazide (HCTZ); (67) uricosuric agents, such as probenecid; (68) enzymes such. . .
DETD . . . the following less common drugs may also be used: Chlorhexidine, estradiol cypionate in oil, estradiol valerate in oil, flurbiprofen, flurbiprofen **sodium**, ivermectin, levodopa, nafarelin, and somatropin.
DETD Further still, the following intravenous products may be used: acyclovir **sodium**, aldesleukin, atenolol, bleomycin sulfate, human calcitonin, salmon calcitonin, carboplatin, carmustine, dactinomycin, daunorubicin HCl, docetaxel, doxorubicin HCl, epoetin alfa, etoposide (VP-16), fluorouracil (5-FU), ganciclovir **sodium**, gentamicin sulfate, interferon alfa, leuprolide acetate, meperidine HCl, methadone HCl, methotrexate **sodium**, paclitaxel, ranitidine HCl, vinblastin sulfate, and zidovudine (AZT).
DETD . . . (NGF); growth hormone releasing factor (GHRF); epidermal growth factor (EGF); fibroblast growth factor homologous factor (FGFHF); hepatocyte growth factor (HGF); **insulin growth factor** (IGF); invasion inhibiting factor-2 (IIF-2); bone morphogenetic proteins 1-7 (BMP 1-7); somatostatin; thymosin-.alpha.-1; .gamma.-globulin; superoxide dismutase (SOD); and complement factors.
DETD Five mg of P(BHET-EP/TC, 80/20) microspheres containing FITC-BSA are suspended in one mL of phosphate **buffer** saline (PBS) at pH 7.4 and placed into a shaker heated to a temperature of about 37.degree. C. At various. . .

DETD Scaling up, about 50 mg of P(BHET-EP/TC, 80/20) microspheres are suspended in vials containing 10 mL of phosphate buffer saline (PBS). The vials are heated in an incubator to a temperature of about 37.degree. C. and then shaken at. . .

L11 ANSWER 2 OF 14 USPATFULL

SUMM . . . hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenyl-propionate, picrate, pivalate, propionate, **succinate**, tartrate, thiocyanate, tosylate and undecanoate. Base salts include **ammonium** salts, alkali metal salts, such as **sodium** and **potassium** salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine,. . .

SUMM . . . utilized in the compositions of this invention. These neurotrophic factors include, but are not limited to, nerve growth factor (NGF), **insulin growth factor** (IGF-1) and its active truncated derivatives such as gIGF-1, acidic and basic fibroblast growth factor (aFGF and bFGF, respectively), platelet-derived. . .

SUMM . . . compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, **buffer** substances such as phosphates, glycine, sorbic acid, **potassium** sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, **potassium** hydrogen phosphate, **sodium** chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, **sodium** carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

SUMM . . . a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic **sodium** chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any. . .

CLM What is claimed is:

9. The method according to claim 8, wherein said neurotrophic factor is selected from nerve growth factor (NGF), **insulin growth factor** (IGF) and active truncated derivatives thereof, acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), platelet-derived growth factors (PDGF),. . .

L11 ANSWER 3 OF 14 USPATFULL

DETD . . . stability. Such materials are non-toxic to recipients at the dosages and concentrations employed and include buffers such as phosphate, citrate, **succinate**, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about. . . derivatives, glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as **sodium**; and/or nonionic surfactants such as polysorbates, poloxmers, or PEG. The IGF-I is typically formulated in such vehicles at a concentration. . .

DETD . . . an acceptable carrier vehicle to form a pharmaceutical composition, preferably one that does not contain cells. In one embodiment, the **buffer** used for formulation will depend on whether the composition will be employed immediately upon mixing or stored for later use.. . . mannitol, glycine, and phosphate at pH 7.4. If this mixture is to be stored, it is preferably formulated in a **buffer** at a pH of about 6, in the optional further presence of a surfactant that increases the solubility of the. . .

DETD . . . or phenol, or both, and the buffered solution is an acetic acid
salt buffered solution. More preferably, the osmolyte is **sodium** chloride and the acetic acid salt is **sodium** acetate. Even more preferably, the amount of IGF-I is about 8-12 mg/mL, the amount of **sodium** chloride is about 5-6 mg/mL, the amount of benzyl alcohol is about 8-10 mg/mL, the amount of phenol is about 2-3 mg/mL, and the amount of **sodium** acetate is about 50 mM so that the pH is about 5.4. Additionally, the formulation can contain about 1-5 mg/mL.

. an amount of about 1-3 mg/mL. Alternatively, the formulation is suitably IGF-I dissolved at 5 mg/ml in 10 mM citrate **buffer** and 126 mM NaCl at pH 6.

DETD . . . tubular changes in late gestation (Nidess et al., J. Urol., 131:156-162 [1984]), and in organ explant are associated with increase **sodium potassium** AtPase activity (Avner et al., Kidney Int., supra). These dilatations regress after birth as the severe terminal change of the. . .

DETD . . . it has been suggested that the function of such a unit in the circulation is as a reservoir and a **buffer** for IGF-I and IGF-II, thereby preventing rapid changes of free IGF.

DETD . . . atrophy model required higher doses of IGF-I, compared with older animals. This may be explained by the relative increase of **insulin growth factor** binding protein-I and the KD 40 complex seen in the fetal and newborn period, which is effective in delivering IGF-I. . .

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SUMM . . . hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, **succinate**, tartrate, thiocyanate, tosylate and undecanoate. Base salts include **ammonium** salts, alkali metal salts, such as **sodium** and **potassium** salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine,. . .

SUMM . . . utilized in the compositions of this invention. These neurotrophic factors include, but are not limited to, nerve growth factor (NGF), **insulin growth factor** (IGF-1) and its active truncated derivatives such as gIGF-1, acidic and basic fibroblast growth factor (aFGF and bFGF, respectively), platelet-derived. . .

SUMM . . . compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, **buffer** substances such as phosphates, glycine, sorbic acid, **potassium** sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, **potassium** hydrogen phosphate, **sodium** chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, **sodium** carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

SUMM . . . a solution in 1,3-butanediol. Among the acceptable vehicles and
solvents that may be employed are water, Ringer's solution and isotonic **sodium** chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any. . .

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DETD . . . stability. Such materials are non-toxic to recipients at the dosages and concentrations employed and include buffers such as phosphate, citrate, **succinate**, acetic acid, and other organic

acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less th[redacted]about. . . derivatives, glu[redacted]e, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol
or sorbitol; counterions such as **sodium**; and/or nonionic surfactants such as polysorbates, poloxmers, or PEG. The IGF-I is typically formulated in such vehicles at a concentration. . .

DETD . . . an acceptable carrier vehicle to form a pharmaceutical composition, preferably one that does not contain cells. In one embodiment, the **buffer** used for formulation will depend on whether the composition will be employed immediately upon mixing or stored for later use.. . . mannitol, glycine, and phosphate at pH 7.4. If this mixture is to be stored, it is preferably formulated in a **buffer** at a pH of about 6, in the optional further presence of a surfactant that increases the solubility of the. . .

DETD . . . or phenol, or both, and the buffered solution is an acetic acid
salt buffered solution. More preferably, the osmolyte is **sodium** chloride and the acetic acid salt is **sodium** acetate. Even more preferably, the amount of IGF-I is about 8-12 mg/mL, the amount of **sodium** chloride is about 5-6 mg/mL, the amount of benzyl alcohol is about 8-10 mg/mL, the amount of phenol is about 2-3 mg/mL, and the amount of **sodium** acetate is about 50 mM so that the pH is about 5.4. Additionally, the formulation can contain about 1-5 mg/mL.

. an amount of about 1-3 mg/mL. Alternatively, the formulation is suitably IGF-I dissolved at 5 mg/ml in 10 mM citrate **buffer** and 126 mM NaCl at pH 6.

DETD . . . changes in late gestation (Nidess et al., J. Urol., 131: 156-162 [1984]), and in organ explant are associated with increase **sodium potassium** AtPase activity (Avner et al.. Kidney Int., supra). These dilatations regress after birth as the severe terminal change of the. . .

DETD . . . it has been suggested that the function of such a unit in the circulation is as a reservoir and a **buffer** for IGF-I and IGF-II, theeby preventing rapid changes of free IGF.

DETD . . . atrophy model required higher doses of IGF-I, compared with older animals. This may be explained by the relative increase of **insulin growth factor** binding protein-I and the KD 40 complex seen in the fetal and newborn period, which is effective in delivering IGF-I. . .

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AB . . . coated cores which includes a pharmaceutically acceptable carrier selected from calcium carbonate, calcium silicate, calcium magnesium silicate, calcium phosphate, kaolin, **sodium** hydrogen carbonate, **sodium** sulfate, barium carbonate, barium sulfate, magnesium sulfate, magnesium carbonate, and activated carbon, and an active substance in a layer on. . .

DETD . . . core, and which is selected from the group consisting of calcium carbonate, calcium silicate, calcium magnesium silicate, calcium
phosphate, kaolin, **sodium** hydrogen carbonate, **sodium** sulfate, barium carbonate, barium sulfate, magnesium sulfate, magnesium carbonate, and activated carbon, and

DETD . . . for use in formulations according to the invention are, e.g., calcium carbonate, calcium silicate, calcium magnesium silicate, calcium
phosphate, kaolin, **sodium** hydrogen carbonate, **sodium** sulfate, barium carbonate, barium sulfate, magnesium sulfate, magnesium carbonate, and activated carbon.

DETD antihypertensive agents such as, e.g., propanolol, metoprolol such as metoprolol tartrate or metoprolol **succinate**, clonidine, pindolol, and the like;

DETD . . . peptide such as, e.g., growth hormone releasing factors, growth

factors. (epidermal growth factor (EGF), nerve growth factor (NGF), TGF, PDGF, **insulin growth factor** (IGF), fibroblast growth factor (aFGF, bFGF. etc.), and the like), somatostatin, calcitonin, insulin, vasopressin, interferons, IL-2, urokinase, serratiopeptidase, superoxide dismutase. . .

DETD . . . a coating based on one or more of the material selected from the following: hydroxypropyl-methylcellulose, ethylcellulose, methylcellulose, hydroxyethylmethylcellulose, hydroxypropylcellulose, carboxymethylcellulose **sodium**, acrylate polymers (such as, e.g. Eudragit.RTM. E), polyethylene glycols and polyvinylpyrrolidone;

DETD . . . the material selected from the following: methacrylic acid copolymers (e.g. Eudragit.RTM. L or S), cellulose acetate phthalate, ethylcellulose, hydroxypropylmethylcellulose acetate **succinate**, polyvinyl acetate phthalate, and shellac; or

DETD . . . (Eudragit.RTM. RL and RS acrylic resins are copolymers of acrylic and methacrylic acid esters with a low content of quaternary **ammonium** groups) poly(methyl methacrylate), methacrylate hydrogels, ethylene glycol methacrylate; polylactide derivatives such as, e.g., dl-polylactic acid, polylactic-glycolic acid copolymer; cellulose derivatives,. . .

DETD . . . core, and which is selected from the group consisting of calcium carbonate, calcium silicate, calcium magnesium silicate, calcium phosphate, kaolin, **sodium** hydrogen carbonate, **sodium** sulfate, barium carbonate, barium sulfate, magnesium sulfate, magnesium carbonate, and activated carbon, and

DETD potato starch, calcium carbonate, **sodium** chloride, lactose, calcium phosphate, calcium sulfate, or **sodium** phosphate;

DETD granulating and disintegrating agents, for example, cellulose derivatives including microcrystalline cellulose, starches including potato starch, croscarmellose **sodium**, alginates, or alginic acid;

DETD binding agents, for example, sucrose, glucose, sorbitol, acacia, alginic acid, **sodium** alginate, gelatin, starch, pregelatinized starch, microcrystalline cellulose, magnesium aluminum silicate, carboxymethylcellulose **sodium**, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, polyvinylpyrrolidone such as, e.g, PVP K12, PVP K15, PVP K17, PVP K25, PVP K30, PVP K60,. . .

DETD . . . agents are, e.g., naturally occurring gums such as, e.g., gum acacia, xanthan gum, or gum tragacanth; celluloses such as, e.g., **sodium** carboxymethylcellulose, microcrystalline cellulose (e.g. Avicel.RTM. RC 591, methylcellulose; alginates such as, e.g., **sodium** alginate, etc.

DETD Examples of chelating agents are **sodium** EDTA, citric acid, and phosphoric acid.

DETD . . . oil, poppyseed oil, rapeseed oil, sesame oil, soybean oil, sunflower oil, and teaseed oil; and of polymers such as carmelose, **sodium** carmelose, hydroxypropylmethylcellulose, hydroxyethylcellylose, hydroxypropylcellulose, chitosane, pectin, xanthan gum, carragenan, locust bean gum, acacia gum, gelatin, and alginates.

DETD **Sodium** carboxymethylcellulose from P. Br.o slashed.ste A/S, Denmark

DETD **Sodium** hydrogen carbonate (serving as a carbon dioxide source for effervescent reaction) from Nordisk Droge Handel A/S, Denmark

DETD

| | |
|---|---|
| Polymer: | ethylcellulose |
| Plasticizer: | DBS (dibutylsebacetate) |
| Stabilizer: | oleic acid |
| Anti-adherent: | fumed silica |
| Aqueous base: | **ammonium** hydroxide solution |
| Total solid content: | 25% w/w |

DETD . . . was employed. The dissolution test was performed in accordance

with USP, method 2 (paddle-method) and 50 rpm using a phosphate **buffer** solution, [redacted]7.5 (USP) as dissolution mediu[redacted]nd a temperature of 37.degree. C. In some cases the dissolution medium was. . .

DETD . . . New Zealand white rabbit SSC: CPH) was fasted for 20 hours before they were killed by means of a pentobarbital **sodium** injection. The intestines of the rabbits were dissected and placed in an isotonic 0.9% **sodium** chloride solution at room temperature (about 18.degree. C.). Within 30 minutes the jejunums were gently rinsed with the saline until. . .

DETD . . . relative humidity was kept at about 100%. The jejunum was then flushed with a medium of 0.02 M isotonic phosphate **buffer** solution (pH 6.5, 37.degree. C.) for 2 minutes at a flow rate of 5 ml/min, using a peristaltic pump. An. . . sample, the area onto which the sample should be applied was marked with indian ink). Optionally, 1 ml of the **buffer** solution was carefully dropped evenly on the sample applied. Immediately after, the segments were left for 10 minutes in the. . . to prevent drying of the mucus. After 10 minutes, the segments were flushed evenly with the isotonic 0.02 M phosphate **buffer** solution (pH 6.5, 37.degree. C.) for 30 minutes at a flow rate of 5 ml/min. The tip of the tube carrying the **buffer** solution was placed 3-4 mm above the jejunum to ensure an even liquid flow over the mucosa. The washings were. . .

DETD . . . each of the vessels a dose corresponding to 300 mg of theophylline of the pellets and 900 ml of phosphate **buffer** solution pH 7.5, USP as dissolution medium.

DETD . . . each of the vessels 1.5 gram (corresponding to 300 mg of theophylline) of the pellets and 900 ml of phosphate **buffer** solution pH 7.5, USP as dissolution medium.

DETD . . . of the 6 vessels 1.5 gram (corresponding to 300 mg of theophylline) of the pellets and 900 ml of phosphate **buffer** solution pH 7.5, USP as dissolution medium.

DETD . . . 20% w/w or 40% w/w

| | | |
|---|---|---|
| II | Microcrystalline cellulose (sieve 710 .mu.m) (Avicel .RTM. 101 or 102) | 60% w/w or 80% w/w |
| III | **Sodium** carboxyrnethylcellulose (sieve 300 .mu.m) | 0.80% w/w |
| IV | Magnesium stearate (sieve 300 .mu.m) | 0.5% w/w |

DETD Composition:

| | | mg/tablet |
|---|---|---|
| I | Pellets from Example 10 | 100 |
| II | Avicel PH 101 | 394 |
| III | **Sodium** carboxymethylcellulose | 3.75 |
| IV | Magnesium stearate | 2.50 |

DETD

| mg/tablet |
|---|
| Pellets from Example 6 219 coated with 50% w/w ethyl-cellulose |

Sorbitol 439.5
Citric acid 439.5
**Sodium** hydrogencarbonate
330.0
Polyethylene glycol 6000
72.0

---

CLM What is claimed is:
. . . core, and which is selected from the group consisting of calcium carbonate, calcium silicate, calcium magnesium silicate, calcium phosphate, kaolin, **sodium** hydrogen carbonate, **sodium** sulfate, barium carbonate, barium sulfate, magnesium sulfate, magnesium carbonate, and activated carbon, and ii) an active drug substance being present. . .
. . . core, and which is selected from the group consisting of calcium carbonate, calcium silicate, calcium magnesium silicate, calcium phosphate, kaolin, **sodium** hydrogen carbonate, **sodium** sulfate, barium carbonate, barium sulfate, magnesium sulfate, magnesium carbonate, and activated carbon, and ii) an active drug substance, the pharmaceutically. . .
. . . core, and which is selected from the group consisting of calcium carbonate, calcium silicate, calcium magnesium silicate, calcium phosphate, kaolin, **sodium** sulfate, barium carbonate, barium sulfate, magnesium sulfate, magnesium carbonate, and activated carbon, and ii) an active drug substance, the pharmaceutically. . .

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DETD iii) flushing the jejunum on the support with 0.02 M isotonic phosphate **buffer** solution (pH 6.5, 37.degree. C.) for 5 min at a flow rate of 10 ml/min,
DETD v) dropping about 1 ml of said phosphate **buffer** solution on the sample applied,
DETD vii) flushing the jejunum with the sample applied with said phosphate **buffer** solution (pH 6.5, 37.degree. C.) for 30 minutes at a flow rate of 10 ml/min,
DETD iii) flushing the jejunum on the support with 0.02 M isotonic phosphate **buffer** solution (pH 6.5, 37.degree. C.) for 5 min at a flow rate of 10 ml/min,
DETD v) dropping about 1 ml of said phosphate **buffer** solution on the sample applied,
DETD vii) flushing the jejunum with the sample applied with said phosphate **buffer** solution (pH 6.5, 37.degree. C.) for 30 minutes at a flow rate of 10 ml/min,
DETD . . . peptide such as, e.g., growth hormone releasing factors, growth factors (epidermal growth factor (EGF), nerve growth factor (NGF), TGF, PDGF, **insulin growth factor** (IGF), fibroblast growth factor (aFGF, bFGF, etc.), and the like), somatostatin, calcitonin, insulin, vasopressin, interferons, IL-2, urokinase, serratiopeptidase, superoxide dismutase. . .
DETD . . . compositions comprising GMO/ethanol/popranolol HCl (80/15/5% w/w), GMO/ethanol/fentanyl citrate (78/20/2% w/w), GMO/ethanol/neomycin sulfate (75/20/5% w/w), GMO/ethanol/phenthermine HCl (60/30/10% w/w), and GMO/ethanol/naproxene **sodium** (70/20/10% w/w) are listed.
DETD inert diluents or fillers, such as sucrose, sorbitol, sugar, mannitol, microcrystalline cellulose, carboxymethylcellulose **sodium**, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, starches including potato starch, calcium carbonate, **sodium** chloride, lactose, calcium phosphate, calcium sulfate or **sodium** phosphate;
DETD granulating and disintegrating agents, for example, cellulose derivatives including microcrystalline cellulose, starches including potato starch, **sodium** starch glycolate, croscarmellose **sodium**, crospovidone, alginates or alginic acid;
DETD binding agents, for example, sucrose, glucose, sorbitol, acacia, alginic

acid, **sodium** alginate, gelatin, starch,
DETD pregelatinized [redacted]rch, microcrystalline cellulos[redacted]magnesium aluminum silicate, carboxymethylcellulose **sodium**, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, or polyethylene glycol; and
DETD . . . or an enteric coating (e.g. based on methacrylic acid copolymer
(Eudragit), cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate **succinate**, polyvinyl acetate phthalate, shellac and/or ethylcellulose). Furthermore, a time delay material such as, e.g., glyceryl monostearate or glyceryl distearate may. . .
DETD Examples of chelating agents are **sodium** EDTA, citric acid and phosphoric acid.
DETD . . . oil, poppyseed oil, rapeseed oil, sesame oil, soybean oil, sunflower oil, and teaseed oil; and of polymers such as carmelose, **sodium** carmelose, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, chitosane, pectin, xanthan gum, carrageenan, locust bean gum, acacia gum, gelatin, and alginates, and solvents such. . .
DETD **Sodium** fluoride available from Sigma Chemical Co., St. Louis
DETD **Sodium** alginate (Sobalg FD 120) available from Grindsted Products A/S, Denmark
DETD . . . New Zealand white rabbit SSC: CPH) was fasted for 20 hours before they were killed by means of a pentobarbital **sodium** injection. The intestines of the rabbits were dissected and placed in an
isotonic 0.9% **sodium** chloride solution at room temperature (about 18.degree. C.). Within 30 minutes the jejunums were cut and washed with 0.9% **sodium** chloride solution. The lumens were gently rinsed with the saline until the intestines were clean. The jejunums were cut into. . .
DETD . . . thermostated cell was kept at about 100%. The jejunum was then flushed with a medium of 0.02 M isotonic phosphate **buffer** solution (pH 6.5, 37.degree. C.) for 2 or 5 minutes (in the following denoted "initial rinsing period") at a flow. . . 10 ml/min (in the following denoted "initial rinsing flow"), respectively, using a peristaltic pump to equilibrate the jejunum with the **buffer** and to rinse off loose mucosa. An accurately weighted amount of the sample to be tested for bioadhesive properties (about 50-150 mg) was placed evenly on the mucosa of the jejunum (about 0.8.times.6 cm). About
1 ml of the **buffer** solution was carefully dropped evenly on the sample applied to ensure formation of such a fluid crystalline phase, if possible. . . to prevent drying of the mucus. After 10 minutes, the segments were flushed evenly with the isotonic 0.02 M phosphate **buffer** solution (pH 6.5, 37.degree. C.) for 15-60 minutes such as, e.g., 30 minutes at a flow rate of 5-15 ml/min such as 10 ml/min (in the Examples denoted "flow rate"). The tip of the tube carrying the **buffer** solution was placed 3-4 mm above the jejunum to ensure an even liquid flow over the mucosa. The washings were. . .
DETD . . . ileum from freshly slaughtered pigs were used. The gut was stored on ice until it was washed with 0.9% w/w **sodium** chloride solution within 2 hours. The lumens were gently rinsed with the
saline until the intestines were clean. The gut. . .
DETD . . . the contact force. In order to moist the tissue and hydrate the
sample, about 0.5 ml isotonic 0.05 M phosphate **buffer**, pH 6.0 was added to the tissue. Such an addition also enables a cubic phase to be formed. The instrument. . .
DETD Similarly, other substances which are known bioadhesive substances are tested such as, e.g., chitosane, tragacanth, hydroxypropylmethylcellulose (HPMC), **sodium** alginate, hydroxypropylcellulose (HPC), karaya gum, carboxymethylcellulose (CMC),

gelatin, pectin, acacia, PEG 6000, povidone, or DEAE-dextran (less bioadhesive tha[redacted]olycarbophil). By. . .

DETD

| Test substance | Work of adhesion (mJ cm.sup.-2) |
|---|---|
| DEAE-dextran | 0.010 |
| **Sodium** alginate | 0.015 |
| GMO/water 85/15% w/w* | 0.028 |
| HPMC | 0.036 |
| Carbopol 934 | 0.031 |
| GMO | 0.047 |
| polycarbophil | 0.060 |

*lamellar phase

DETD . . . i.d.) was packed with Supelcosil LC-18-DM and was eluted isocratically at ambient temperature with a mobile phase consisting of methanol:water:acetate **buffer** (pH 3.5) (840:120:40 v/v). However, in some cases interference from other substance may occur and then it may be necessary. . .

DETD . . . 78

| | |
|---|---|
| GMO/ethanol/burprenorfin: | |
| 59.4/39/6/1 | 85 |
| 58.8/39.2/2 | 71 |
| GMO/ethanol/estradiol: | |
| 59.4/39.6/1 | 87* |
| 58.2/38.8/3 | 77 |
| GMO/ethanol/progesterone: | |
| 59.4/39.6/1 | 104 |
| 58.2/38.8/3 | 103 |
| 57/38/5 | 98 |
| GMO/ethanol/indomethacin: | |
| 58.2/38.8/2 | 91 |
| 57/38/5 | 98 |
| 54/36/10 | 25 |
| GMO/ethanol/nifedipine: | |
| 58.2/38.8/2 | 94 |
| GMO/ethanol/triclosan: | |
| 59.4/39.6/1 | 101 |
| 58.2/3.8.8/3 | 109 |
| 57/38/5 | 105 |
| GMO/acyclovir**: | |
| 9.8/2 | 108 |
| 95/5 | 108 |
| GMO/ethanol/isosorbid mononitrate: | |
| 58.8/39.2/2 | 84 |
| 57/38/5 | 81 |
| 54/36/10 | 32 |
| GMO/**sodium** fluoride**: | |
| 98/2 | 87 |
| 95/5 | 76 |
| GMO/prochlorperazin**: | |
| 98/2 | 78 |
| 95/5 | 90 |

*recovery was determined to be 79%

**the compositions were suspensions

DETD Mobile phase: Methanol R: **Buffer** (85:15)

DETD **Buffer**: 0.05 M NH.sub.4 H.sub.2 PO.sub.4 (5.75 g in 1000 ml H.sub.2 O)

DETD . . . application, the membrane was pretreated and thoroughly rinsed with distilled water. As receptor medium was used an isotonic 0.05M phosphate **buffer** pH 6.3 (Danish Drug Standards, DLS) and the medium was magnetically stirred at 300 rpm.

DETD . . . taken to ensure a homogenous distribution of the composition on

the total area of the membrane available for diffusion. Phosphate **buffer** was then l[redacted]ed into the receptor part (tim[redacted]=0) and at appropriate time intervals, samples of 1 ml were withdrawn. . .

DETD Mobile phase: Methanol R: Water: **Buffer** (840:120:40)

DETD Preparation of **buffer** solution:

DETD Weigh out 13.33 g **sodium** acetate (CH.sub.3 COONa, 3H.sub.2 O) in a 1000 ml volumetric flask and dissolve in 500 ml of water. Add 5.8. . .

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SUMM . . . hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenyl-propionate, picrate, pivalate, propionate, **succinate**, tartrate, thiocyanate, tosylate and undecanoate. Base salts include **ammonium** salts, alkali metal salts, such as **sodium** and **potassium** salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine,. . .

SUMM . . . invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, **buffer** substances such as phosphates, glycine, sorbic acid, **potassium** sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, **potassium** hydrogen phosphate, **sodium** chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, **sodium** carboxymethyl cellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

SUMM . . . a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic **sodium** chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any. . .

SUMM . . . neurotrophic use, the compounds of this invention may be combined with other neurotrophic factors, such as nerve growth factor (NGF), **insulin growth factor** (IGF-1) and its active truncated derivatives such as gIGF-1, acidic and basic fibroblast growth factor (aFGF and bFGF, respectively), platelet-derived. . .

DETD . . . toluene (30 mL) was successively added the boronic acid (137)(420 mg, 2 mmole) dissolved in 2 ml of ethanol and **sodium** carbonate (420 mg, 4 mmole) dissolved in 2 ml of H.sub.2 O. The resulting solution was heated at reflux for. . .

DETD To a solution of the ketone (140) (210 mg, 0.54 mmole) in methanol (10 mL) at 0.degree. C. was added **sodium** borohydride (30 mg, 0.79 mmole), and the mixture stirred at room temperature for 20 min. The reaction mixture was quenched. . .

DETD To a suspension of **sodium** hydride (18.6 g as an 80% dispersion in mineral oil, 0.62 mol) in anhydrous THF (80 mL) was added ethanol.

.

DETD . . . toluene (100 mL) was successively added the boronic acid (154)(2.57 g, 10.8 mmole) dissolved in 7 mL of ethanol and **sodium** carbonate monohydrate (2.74 g, 22.1 mmole) dissolved in 4 mL of H.sub.2 O. The resulting solution mixture was heated at. . .

DETD . . . (0.55 g, 0.48 mmol) in toluene (300 mL) was added 154 (5.00 g, 21.0 mmol) in ethanol (20 mL) and **sodium** carbonate monohydrate (5.20 g, 42 mmol) in water 20 mL). The solution was heated at reflux for 16 hours and. . .

DETD . . . was filtered through celite and partitioned with water and ethyl acetate. The organic phase was washed two times with aqueous

**potassium** bisulfate, two times with aqueous **sodium** bicarbonate, two times with water, once with brine and dried over magnesium sulfate. The solvent was evaporated under reduced pressure.

DETD . . . dropwise. The mixture was allowed to warm to -30.degree. C. and stir for 1/2 hour. Reaction was quenched with aqueous **ammonium** chloride and extracted with ethyl acetate. The organic phase was washed once with brine and dried over magnesium sulfate. The. . .

DETD . . . stirred for twenty minutes at 0.degree. C. The reaction was diluted with methylene chloride and washed two times with aqueous **potassium** bisulfate, two times with water, once with brine and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. . .

DETD . . . mmole) of 168 in THF (3 ml). The mixture was stirred for fifteen minutes and was slowly quenched with aqueous **sodium** sulfate, then warmed to room temperature and treated with excess of **sodium** sulfate powder. The mixture was stirred for fifteen minutes and filtered. The solvent was evaporated under reduced pressure and the. . .

DETD To a stirred mixture of 62 mg (2.6 mmole) of **sodium** hydride in THF (6 ml) at 0.degree. C. was added 0.86 g (2.0 mmole) of 169. The mixture stirred for. . .

DETD . . . dissolved in THF (4 ml). The mixture was allowed to stir for two hours and was slowly quenched with aqueous **sodium** sulfate, then warmed to room temperature and and treated with excess of **sodium** sulfate powder. The mixture was stirred for fifteen minutes and filtered. The solvent was evaporated under reduced pressure to give. . .

DETD . . . The reaction was allowed to stir at room temperature overnight, diluted with methylene chloride and washed two times with aqueous **sodium** bicarbonate, two times with water, once with brine, and dried over **sodium** sulfate. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel using diethyl. . .

DETD . . . dissolved in diethyl ether (1 ml). The mixture was allowed to stir for two minutes and was quenched with aqueous **sodium** sulfate, then warmed to room temperature and treated with excess of **sodium** sulfate powder. The mixture was stirred for fifteen minutes and filtered. The solvent was evaporated under reduced pressure and the. . .

DETD . . . tert-butylmagnesium chloride in THF. The reaction was allowed to stir at 0.degree. C. for fifteen minutes and quenched with aqueous **ammonium** chloride. The aqueous phase was extracted three times with methylene chloride. The organic layers were combined and washed once with. . .

DETD . . . hydroxide. The reaction was allowed to warm to room temperature and stir for four hours, then acidified with 10% aqueous **potassium** bisulfate, and extracted three times with methylene chloride. The organic layers were combined and washed once with brine, dried over. . .

DETD . . . two hours and then warmed to room temperature. The organic phase was washed three times with ethylene glycol dried over **sodium** sulfate to give 20 g of 176. ##STR49##

DETD . . . to 0.degree. C. and acidified with 0.5N aqueous hydrochloric acid, washed organic phase two times with water, once with aqueous **sodium** bicarbonate, two times with water, once with brine, and dried over **sodium** sulfate. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica using 9:1 hexane/ethyl. . .

DETD . . . organic phase was cooled to 0.degree. C., subjected to a stream of nitrogen for 0.5 hours and then dried over **sodium** sulfate.

The solvent was evaporated under reduced pressure to give 95 mg or 178.
##STR51##

DETD . . . mmol) of 1,3-1-benzenedemethanol (Aldrich Chemical Co.) in 500 mL of dry THF was added 7.76 g (232 mmol) of 80% **sodium** hydride. To this suspension was added 34.97 (232 mmol) of tert-butyldimethylsilyl chloride and the resulting mixture was allowed to stir. . .

DETD . . . CH.sub.2 Cl.sub.2 at 0.degree. C. was added 350 mg (2.2 mmol) of TEMPO, 295 mL (197 mmol) of 0.67 M **sodium** hypochlorite containing 7.5 g of **sodium** bicarbonate and 1.34 g (13.1 mmol) of **sodium** bromide. The resulting mixture was allowed to stir at 0.degree. C. for 0.5 h and then extracted into ethyl acetate. The organic phase was washed sequentially with aqueous solutions of **potassium** iodide and **sodium** thiosulfate and then dried over MgSO.sub.4 and concentrated. Flash chromatography (elution with 20% ethyl acetate in hexane) gave 31.4 g. . .

CLM What is claimed is:
12. The composition according to claim 11, wherein said neurotrophic factor is selected from nerve growth factor (NGF), **insulin growth factor** (IGF) and active truncated derivatives thereof, acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), platelet-derived growth factors (PDGF),. . .
15. The method according to claim 14, wherein said neurotrophic factor is selected from nerve growth factor (NGF), **Insulin growth factor** (IGF) and active truncated derivatives thereof, acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), platelet-derived growth factors (PDGF),. . .

L11 ANSWER 9 OF 14 USPATFULL

SUMM . . . hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenyl-propionate, picrate, pivalate, propionate, **succinate**, tartrate, thiocyanate, tosylate and undecanoate. Base salts include **ammonium** salts, alkali metal salts, such as **sodium** and **potassium** salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine,. . .

SUMM . . . utilized in the compositions of this invention. These neurotrophic factors include, but are not limited to, nerve growth factor (NGF), **insulin growth factor** (IGF-1) and its active truncated derivatives such as gIGF-1, acidic and basic fibroblast growth factor (aFGF and bFGF, respectively), platelet-derived. . .

SUMM . . . compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, **buffer** substances such as phosphates, glycine, sorbic acid, **potassium** sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, **potassium** hydrogen phosphate, **sodium** chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, **sodium** carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

SUMM . . . a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic **sodium** chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any. . .

DETD . . . mixture was cooled and concentrated. The residue was taken up

into ethanol (50 mL) and added to a slurry of **sodium** borohydride (2.[redacted]g, 77.8 mmol) in ethanol (50 m[redacted]and the mixture heated to 80.degree. C. and stirred for 1. . . . with 6N hydrochloric acid. The aqueous phase was washed with ethyl acetate (2.times.). The aqueous phase was made basic with **sodium** hydroxide to a pH of 10 and the product extracted with methylene chloride (2.times.). The organics were combined, washed with. . .

DETD . . . water. The layers were separated and the aqueous phase reextracted with ethyl acetate. The organics were combined, washed with saturated **sodium** bicarbonate, water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Chromatography of the residue over silica. . .

DETD . . . After stirring at room temperature for 1.5 h, the reaction was concentrated in vacuo. The residue was neutralized with saturated **potassium** carbonate and extracted with ethyl acetate (2.times.). The extracts were combined, washed with water, dried over anhydrous magnesium sulfate, filtered. . .

DETD . . . water. The layers were separated and the aqueous phase reextracted with ethyl acetate. The organics were combined, washed with saturated **sodium** bicarbonate, water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The residue was chromatographed on silica. . .

DETD To a solution of 1,7-di(pyridin-4-yl)-heptan-4-ol (4.1 g, 15.2 mmol) in methylene chloride (50 mL) at 0.degree. C., was added **potassium** bromide (180 mg) and 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (71 mg). To the resulting mixture was added dropwise a solution of **sodium** bicarbonate (510 mg) in **sodium** hypochlorite (65 ml). After the addition was complete, the reaction mixture was warmed to room temperature and stirred for 30. . .

DETD To a slurry of methylamine hydrochloride (1.7 g, 25.4 mmol) and **sodium** acetate (2.5 g, 30.48 mmol) in methanol (20 mL) was added a solution of compound 2 (1.21 g, 5.08 mmol) in methanol (5 mL). The resulting mixture was treated with a solution of **sodium** cyanoborohydride (370 mg, 6.09 mmol) in methanol (5 mL) and heated to 80.degree. C. After 1 h at 80.degree. C.,. . . reaction was cooled to room temperature and concentrated in vacuo. The residue was taken up into methylene chloride and 2N **sodium** hydroxide. The layers were separated and the organic phase washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. . .

DETD . . . then allowed to warm to room temperature. After 5 hours, the reaction was diluted with methylene chloride, washed with 1N **sodium** hydroxide, brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to provide a white solid. This material was. . . to 80.degree. C., stirred for 1 hr, cooled to 0.degree. C. and quenched by addition of water (0.5 mL), 15% **sodium** hydroxide (0.5 mL) and an additional 1.5 mL of water. The reaction was diluted with ethyl acetate, dried over anhydrous. . .

DETD To a solution of 1,5-Diphenylpentan-3-one (5.26 g, 22.1 mmol), **ammonium** acetate (8.52 g, 110.5 mmol) and **sodium** acetate (9.06 g, 110.5 mmol) in methanol (80 mL) was added a solution of **sodium** cyanoborohydride (1.67 g, 26.52 mmol) in methanol (20 mL) and the reaction heated to reflux. After stirring at reflux for 30 min, the reaction was cooled and concentrated to dryness. The residue was partioned between methylene chloride and 2N **sodium** hydroxide. The organic phase was separated, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Chromatography. . . mmol) and the reaction heated to 50.degree. C. After stirring for 2 hr, the resulting homogeneous solution was treated with **sodium** borohydride (400 mg, 10.58 mmol) and allowed to stir overnight. The reaction was concentrated to dryness and the residue was partioned between methylene chloride and 2N **sodium** hydroxide. The organic phase was separated, washed with brine, dried over anhydrous

magnesium sulfate, filtered and concentrated in vacuo. Chromatography. . . .

CLM What is claimed is:

. . . 8. The pharmaceutically acceptable composition according to claim 1, wherein said neurotrophic factor is selected from nerve growth factor (NGF), **insulin growth factor** (IGF) and active truncated derivatives thereof, acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), platelet-derived growth factors (PDGF),. . .

20. The method according to claim 19, wherein said neurotrophic factor is selected from nerve growth factor (NGF), **insulin growth factor** (IGF) and active truncated derivatives thereof, acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), platelet-derived growth factors (PDGF),. . .

25. The method according to claim 24, wherein said neurotrophic factor is selected from nerve growth factor (NGF), **insulin growth factor** (IGF) and active truncated derivatives thereof, acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), platelet-derived growth factors (PDGF),. . .

L11 ANSWER 10 OF 14 USPATFULL

SUMM . . . hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, 3-phenyl-propionate, picrate, pivalate, propionate, **succinate**, tartarate, thiocyanate, tosylate and undecanoate. Base salts include **ammonium** salts, alkali metal salts, such as **sodium** and **potassium** salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine,. . .

SUMM . . . utilized in the compositions of this invention. These neurotrophic factors include, but are not limited to, nerve growth factor (NGF), **insulin growth factor** (IGF-1) and its active truncated derivatives such as gIGF-1, acidic and basic fibroblast growth factor (aFGF and bFGF, respectively), platelet-derived. . .

SUMM . . . compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, **buffer** substances such as phosphates, glycine, sorbic acid, **potassium** sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, **potassium** hydrogen phosphate, **sodium** chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, **sodium** carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

SUMM . . . a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic **sodium** chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any. . .

DETD To a solution of 7-hydroxy-1-tetralone (15.0 g, 92.59 mmol) in dimethylsulfoxide (150 mL) was added in portions powdered **potassium** carbonate (30.66 g, 0.11 mol) followed by the addition of 4-picoyl chloride hydrochloroide (18.22 g, 0.22 mol). The resulting mixture. . .

DETD . . . dropwise a 1M solution of diisobutylaluminum hydride in toluene (97.3 mL). After 1 hr, the reaction was quenched with aqueous **potassium sodium** tartrate and diluted with ethyl

acetate followed by warming to room temperature. After stirring for an additional hour[redacted]he layers. . .

DETD To a solution of Compound 3(R) (6.1 g, 20.9 mmol) in methanol (35 mL) was added powdered **potassium** carbonate (2.88 g, 20.9 mmol). After stirring for 45 min, the reaction was concentrated in vacuo. The residue was taken-up. . .

DETD . . . The layers were separated and the aqueous phase was re-extracted with ethyl acetate. The extracts were combined, washed with sat. **sodium** bicarbonate, water, brine, dried over anh. magnesium sulfate, filtered and concentrated in vacuo. Chromatography of the residue on silica gel. . .

DETD . . . (241 mg, 0.21 mmol). After 1 hr, the heterogenous mixture was diluted with ethyl acetate, washed with 50% brine, 5% **sodium** bicarbonate, brine, dried over anh. magnesium sulfate, filtered and concentrated in vacuo. Chromatography of the residue on silica gel (elution. . .

DETD . . . The layers were separated and the aqueous phase was re-extracted with ethyl acetate. The extracts were combined, washed with sat. **sodium** bicarbonate, water, brine, dried over anh. magnesium sulfate, filtered and concentrated in vacuo. Chromatography of the residue on silica gel. . .

DETD . . . 1 (1.71 g, 6.75 mmol) and methoxyamine hydrochloride (845 mg, 10.12 mmol) in abs. ethanol (20 mL) was added powdered **potassium** carbonate (2.25 g, 16.88 mmol) and the reaction heated to reflux. After 2 hr, the reaction was cooled and concentrated in vacuo. The residue was diluted with ethyl acetate, washed with 5% **sodium** bicarbonate, water, brine, dried over anh. magnesium sulfate, filtered and concentrated in vacuo. Chromatography of the residue on silica gel. . .

DETD . . . (10 mL) and washed with diethyl ether (3.times. 20 mL). The aqueous phase was adjusted to pH 8.0 with sat. **sodium** bicarbonate and extracted with ethyl acetate (3.times. 50 mL).

DETD . . . was cooled and concentrated in vacuo. The residue was taken-up into ethanol (5 mL) and added to a slurry of **sodium** boroydride (246 mg, 6.48 mmol) in ethanol (15 mL). The reaction was heated to 80.degree. C., stirred for 30 min,. . . slow addition of 1N hydrochloric acid. The layers were separated. The aqueous phase was adjusted to pH 7 with 2N **sodium** hydroxide and extracted with methylene chloride (2.times.). The organics were combined, washed with brine, dried over anh. magnesium sulfate, filtered. . .

DETD . . . The layers were separated and the aqueous phase was re-extracted with ethyl acetate. The extracts were combined, washed with sat. **sodium** bicarbonate, water, brine, dried over anh. magnesium sulfate, filtered and concentrated in vacuo. Chromatography of the residue on silica gel. . .

DETD . . . trifluoroacetic acid (1 mL). After stirring for 1.5 hr,the reaction was concentrated in vacuo. The residue was neutalized with sat. **potassium** carbonate and extracted with ethyl acetate (2.times.). The extracts were combined washed with brine, dried over anh. magnesium sulfate, filtered. . .

DETD . . . mmol) and propanoic triphenylphosphonium bromide (14.4 g, 34.9 mmol) in methylene chloride (40 mL) at 0.degree. C. was added 1.0M **potassium** t-butoxide in tetrahydrofuran (70 mmol). The reaction was allowed to warm to room temperature and stirred for 2 hr. The. .

DETD . . . (3.5 mL, 25 mmol). After 15 min, the reaction was cooled, diluted with ethyl acetate and washed with water, 10% **sodium** bicarbonate, brine, dried over anh. magnesium sulfate, filtered and

concentrated in vacuo. Chromatography of the residue on silica gel (elution. . .

DETD . . . g of diol. This material was dissolved in 2-butanone (25 mL), treated with 1-bromopropane (6.6 mL, 72.6 mmol) and powdered **potassium** carbonate (9.68 g, 72.6 mmol) and heated to reflux. After 12 hr the reaction was cooled, diluted with water and. . .

DETD . . . of Compound 24 (3.42 g, 12.4 mmol) and 3-pyridinecarboxadehyde (1.59 g, 14.9 mmol) in abs. ethanol (25 mL) was added **potassium** hydroxide (350 mg, 6.2 mmol) and the reaction allowed to stir for 15 min. The reaction was concentrated and the. . .

DETD To a solution of Compound 26 (1.10 g, 2.98 mmol) in abs. methanol (10 mL) was slowly added **sodium** borohydride (226 mg, 2.98 mmol). After stirring for 1 hr, the reaction was concentrated and the residue partitioned between ethyl. . .

CLM What is claimed is:

. . . 9. The pharmaceutically acceptable composition according to claim 1, wherein said neurotrophic factor is selected from nerve growth factor (NGF), **insulin growth factor** (IGF) and active truncated derivatives thereof, acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), platelet-derived growth factors (PDGF),. . .

25. The method according to claim 24, wherein said neurotrophic factor is selected from nerve growth factor (NGF), **insulin growth factor** (IGF) and active truncated derivatives thereof, acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), platelet-derived growth factors (PDGF),. . .

30. The method according to claim 29, wherein said neurotrophic factor is selected from nerve growth factor (NGF), **insulin growth factor** (IGF) and active truncated derivatives thereof, acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), platelet-derived growth factors (PDGF),. . .

L11 ANSWER 11 OF 14 USPATFULL

SUMM . . . hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, **succinate**, tartrate, thiocyanate, tosylate and undecanoate. Base salts include **ammonium** salts, alkali metal salts, such as **sodium** and **potassium** salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine,. . .

SUMM . . . utilized in the compositions of this invention. These neurotrophic factors include, but are not limited to, nerve growth factor (NGF), **insulin growth factor** (IGF-1) and its active truncated derivatives such as gIGF-1, acidic and basic fibroblast growth factor (aFGF and bFGF, respectively), platelet-derived. . .

SUMM . . . compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, **buffer** substances such as phosphates, glycine, sorbic acid, **potassium** sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, **potassium** hydrogen phosphate, **sodium** chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, **sodium** carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

SUMM . . . a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic

**sodium** chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any. . .

DETD . . . (HCl) and washed with EtOAc (2.times.). The pH of the aqueous layer was adjusted to pH>8 by addition of 3N **sodium** hydroxide (NaOH) and then extracted with EtOAc (2.times.). The extracts were combined, washed with half-saturated aqueous **sodium** chloride, brine, dried over magnesium sulfate (MgSO.sub.4), filtered and concentrated. The residue was passed through a plug of silica gel. .

.

DETD . . . room temperature and allowed to stir for 16 h. The reaction was

diluted with EtOAc, washed with water, 5% aqueous **sodium** bicarbonate (NaHCO.sub.3), brine, dried over anhydrous magnesium sulfate

(MgSO.sub.4) and concentrated to provide 16.67 g of compound 3 as a. .

.

CLM What is claimed is:

8. The method according to claim 7, wherein said neurotrophic factor is selected from nerve growth factor (NGF), **insulin growth factor** (IGF) and active truncated derivatives thereof, acidic fibroblast growth factor (aFGF), basic fibroblast growth

factor (bFGF), platelet-derived growth factors (PDGF),. . .

13. The method according to claim 12, wherein said neurotrophic factor is selected from nerve growth factor (NGF), **insulin growth factor** (IGF) and active truncated derivatives thereof, acidic fibroblast growth factor (aFGF), basic fibroblast growth

factor (bFGF), platelet-derived growth factors (PDGF),. . .

L11 ANSWER 12 OF 14 USPATFULL

SUMM . . . hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenyl-propionate, picrate, pivalate, propionate, **succinate**, tartrate, thiocyanate, tosylate and undecanoate. Base salts include **ammonium** salts, alkali metal salts, such as **sodium** and **potassium** salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine,. . .

SUMM . . . invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, **buffer** substances such as phosphates, glycine, sorbic acid, **potassium** sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, **potassium** hydrogen phosphate, **sodium** chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, **sodium** carboxymethyl cellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

SUMM . . . a solution in 1,3-butanediol. Among the acceptable vehicles and

solvents that may be employed are water, Ringer's solution and isotonic **sodium** chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any. . .

SUMM . . . neurotrophic use, the compounds of this invention may be combined with other neurotrophic factors, such as nerve growth factor (NGF), **insulin growth factor** (IGF-1) and its active truncated derivatives such as gIGF-1, acidic and basic fibroblast growth factor (aFGF and bFGF, respectively), platelet-derived. . .

DETD . . . toluene (30 mL) was successively added the boronic acid

(137)(420 mg, 2 mmole) dissolved in 2 ml of ethanol and **sodium** carbonate (420 mg, 4 mmole) dissolved in 2 ml of H.sub.2 O. The resulting solution was heated at reflux for. . .

DETD To a solution of the ketone (140)(210 mg, 0.54 mmole) in methanol (10 mL) at 0.degree. C. was added **sodium** borohydride (30 mg, 0.79 mmole), and the mixture stirred at room temperature for 20 min. The reaction mixture was quenched. . .

DETD To a suspension of **sodium** hydride (18.6 g as an 80% dispersion in mineral oil, 0.62 mol) in anhydrous THF (80 ml) was added ethanol.

. .

DETD . . . toluene (100 mL) was successively added the boronic acid (154)(2.57 g, 10.8 mmole) dissolved in 7 mL of ethanol and **sodium** carbonate monohydrate(2.74 g, 22.1 mmole) dissolved in 4 mL of H.sub.2 O. The resulting solution mixture was heated at reflux.

. .

DETD . . . (0.55 g, 0.48 mmol) in toluene (300 mL) was added 154 (5.00 g, 21.0 mmol) in ethanol (20 mL) and **sodium** carbonate monohydrate (5.20 g, 42 mmol) in water (20 mL). The solution was heated at reflux for 16 hours and. . .

DETD . . . as filtered though celite and partitioned with water and ethyl acetate. The organic phase was washed two times with aqueous **potassium** bisulfate, two times with aqueous **sodium** bicarbonate, two times with water, once with brine and dried over magnesium sulfate. The solvent as evaporated under reduced pressure. .

.

DETD . . . dropwise. The mixture was allowed to warm to -30.degree. C. and

stir for 1/2 hour. Reaction was quenched with aqueous **ammonium** chloride and extracted with ethyl acetate. The organic phase was washed once with brine and dried over magnesium sulfate. The. . .

DETD . . . stirred for twenty minutes at 0.degree. C. The reaction was diluted with methylene chloride and washed two times with aqueous **potassium** bisulfate, two times with water, once with brine and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. . .

DETD . . . mmole) of 168 in THF (3 ml). The mixture was stirred for fifteen minutes and was slowly quenched with aqueous **sodium** sulfate, then warmed to room temperature and treated with excess of **sodium** sulfate powder. The mixture was stirred for fifteen minutes and filtered. The solvent was evaporated under reduced pressure and the. . .

DETD To a stirred mixture of 62 mg (2.6 mmole) of **sodium** hydride in THF (6 ml) at 0.degree. C. was added 0.86 g (2.0 mmole) of 169. The mixture stirred for. . .

DETD . . . dissolved in THF (4 ml). The mixture was allowed to stir for two hours and was slowly quenched with aqueous **sodium** sulfate, then warmed to room temperature and and treated with excess of **sodium** sulfate powder. The mixture was stirred for fifteen minutes and filtered. The solvent was evaporated under reduced pressure to give. . .

DETD . . . The reaction was allowed to stir at room temperature overnight,

diluted with methylene chloride and washed two times with aqueous **sodium** bicarbonate, two times with water, once with brine, and dried over **sodium** sulfate. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel using diethyl. . .

DETD . . . dissolved in diethyl ether (1 ml). The mixture was allowed to stir for two minutes and was quenched with aqueous **sodium** sulfate, then warmed to room temperature and treated with excess of **sodium** sulfate powder. The mixture was stirred for fifteen minutes and filtered. The solvent was evaporated under reduced pressure and the. . .

DETD . . . tert-butylmagnesium chloride in THF. The reaction was allowed

to stir at 0.degree. C. for fifteen minutes and quenched with aqueous **ammonium** chloride. The aqueous phase was extracted three times with methylene chloride. The organic layers were combined and washed once with. . .

DETD . . . hydroxide. The reaction was allowed to warm to room temperature and stir for four hours, then acidified with 10% aqueous **potassium** bisulfate, and extracted three times with methylene chloride. The organic layers were combined and washed once with brine, dried over. . .

DETD . . . two hours and then warmed to room temperature. The organic phase was washed three times with ethylene glycol dried over **sodium** sulfate to give 20 g of 176. ##STR49##

DETD . . . to 0.degree. C. and acidified with 0.5N aqueous hydrochloric acid, washed organic phase two times with water, once with aqueous **sodium** bicarbonate, two times with water, once with brine, and dried over **sodium** sulfate. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica using 9:1 hexane/ethyl. . .

DETD . . . organic phase was cooled to 0.degree. C., subjected to a stream of nitrogen for 0.5 hours and then dried over **sodium** sulfate. The solvent was evaporated under reduced pressure to give 95 mg of 178. ##STR51##

DETD . . . mmol) of 1,3-benzenedemethanol (Aldrich Chemical Co.) in 500 ml of dry THF was added 7.76 g (232 mmol) of 80% **sodium** hydride. To this suspension was added 34.97 g (232 mmol) of tert-butyldimethylsilyl chloride and the resulting mixture was allowed to.

.

DETD . . . of CH.sub.2 Cl.sub.2 at 0.degree. C. was added 350 mg (2.2 mmol) of TEMPO, 295 mL (197 mmol) of 0.67M **sodium** hypochlorite containing 7.5 g of **sodium** bicarbonate and 1.34 g (13.1 mmol) of **sodium** bromide. The resulting mixture mixture was allowed to stir at 0.degree. C. for 0.5 h and then extracted into ethyl acetate. The organic phase was washed sequentially with aqueous solutions of **potassium** iodide and **sodium** thiosulfate and then dried over MgSO.sub.4 and concentrated. Flash chromatography (elution with 20% ethyl acetate in hexane) gave 31.4 g. . .

L11 ANSWER 13 OF 14 USPATFULL

SUMM . . . hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenyl-propionate, picrate, pivalate, propionate, **succinate**, tartrate, thiocyanate, tosylate and undecanoate. Base salts include **ammonium** salts, alkali metal salts, such as **sodium** and **potassium** salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine,. . .

SUMM . . . utilized in the compositions of this invention. These neurotrophic factors include, but are not limited to, nerve growth factor (NGF), **insulin growth factor** (IGF-1) and its active truncated derivatives such as gIGF-1, acidic and basic fibroblast growth factor (aFGF and bFGF, respectively), platelet-derived. . .

SUMM . . . compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, **buffer** substances such as phosphates, glycine, sorbic acid, **potassium** sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, **potassium**

hydrogen phosphate, **sodium** chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, **sodium** carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

SUMM . . . a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic **sodium** chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any. . .

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SUMM . . . upon the pituitary to cause release of growth hormone. The pituitary is maintained under negative feedback control by somatostatin and **insulin growth factor** (IGF). GRF has been found to be enormously active, exhibiting an ED.sub.50 of approximately 50 fmole/ml or 75 pg/ml and. . .

DETD . . . citric acid (ice cold). The organic phase is washed twice with water (15 ml each) and then dried over anhydrous **sodium** sulfate. In order to avoid any detritylation of the product, about 0.3 ml of pyridine is added to the methylene. . .

DETD . . . The organic mixture is extracted with saturated brine (4 times, 75 ml). The ethyl acetate phase is dried over anhydrous **sodium** sulfate. The solution is concentrated in an oil and then redissolved in dry ethyl acetate to obtain 50 ml of. . .

DETD . . . thiophenol for 30 minutes at room temperature. The resin was filtered, washed with methanol (4.times.2 ml) and hydrolyzed with concentrated **ammonium** hydroxide for 17 hours at 50.degree. C. The resin was pelleted and the supernatant concentrated under vacuum and redissolved in. . .

DETD c: Loading of **succinate** 7 on to the aminomethyl polystyrene 5 and masking of any unreacted amino group with acetic anhydride-pyridine

DETD The aforesaid suitably protected mono-dinucleotides were synthesized according to procedures known in the art with slight modifications. 3'-**succinate** 7 of 5'-dimethoxytrityl-thymidine 6 was prepared according to the method published by Miyoshi et al., Nucleic Acids Research, 8, 5491. . .

DETD A slurry of commercially available chloromethyl polystyrene (1% cross linked, 0.32 mmol/g Cl.sup.-) (30 g, 9 mmol) and **potassium** phthalimide (2.77 g, 15 mmol) in DMF 250 ml) was heated at 120.degree. for 20 hours. The resin was then. . .

DETD . . . purified by electrophoresis on an acrylamide gel in the presence of 7M urea. The slowest moving band was isolated by **buffer** elution and after labelling the 5'-hydroxyl group with .gamma.[.sup.32 P]-ATP, the sequence of the heptadecanucleotide fragment 3, was confirmed by. . .

DETD . . . C. for 5 min. followed by the addition of 5 .mu.l of 10 mg/ml tRNA, and 190 .mu.l of 5M **ammonium** acetate. The nucleic acids were ethanol precipitated, resuspended in 200 .mu.l of 0.3M **sodium** acetate, ethanol precipitated again, dried under a vacuum and resuspended in 10 .mu.l of 1 mM Tris(pH 7.4), 0.1 mM. . .